REMARKS

Status of the Claims

Applicants believe that the following accurately represents the status of the claims.

Claims 1-2 and 4-45 are pending. Claim 3 is canceled and new claims 43-45 are added.

Claims 1, 16-17, 28-31, and 33, and 35-42 are withdrawn by the Examiner following a lack of unity holding in the Office Action of March 13, 2007 with traverse by Applicants for reasons as indicated below.

Claims 2-15, 18-27, and 32 have been examined. Applicants note that claims 11-15, 18-27, and 32 have been objected to for improper form and therefore not yet further examined on the merits. However, upon entry of this amendment to place the claims in proper format according to US practice, Applicants believe they are entitled to further examination of claims 11-15, 18-27, and 32 based on the grouping together of claims 2-15, 18-27, and 32 in Group II in the lack of unity holding on page 3 of the Office Action of March 13, 2007. Therefore, the current status of claims 11-15, 18-27, and 32 (in response to the March 13, 2007 Office Action Summary) is "examined and objected to" rather than withdrawn. Applicants respectfully request confirmation in the next Office Action.

The status of claim 34 is unclear from the March 13, 2007 Office Action. Claim 34 was not included in the Restriction Requirement of August 1, 2006. Applicants requested clarification of the status of claim 34 in the response dated October 16, 2006. However, claim 34 was omitted from the grouping of claims for restriction purposes in the March 13, 2007. Therefore, Applicants repeat their request for clarification of the status of claim 34. Since claim

34 was not included in the grouping of claims on page 3 of the March 13, 2007 Office Action and no basis for withdrawal has been given, Applicants have used the status identifier of "original" in the listing of claims.

Support for Amendments

The abstract is amended for grammatical purposes and to include reference to SEQ ID NO:1 as suggested by the Office Action. Support can be found in the original abstract and the specification as filed, for example, at page 4, line 25 through page 5, line 6.

The specification is amended on page 19 by addition of sequence identifiers "19" and "35" in order to comply with USPTO requirements. The Sequence Listing is amended to add SEQ ID NO:35 in order to comply with USPTO requirements. Support for SEQ ID NO: 35 can be found on page 24, line 21 of the specifiation which discloses "YGPTE".

Claims 11, 14, 18, 21, 22, 24, 26, and 32 are amended to remove improper multiple dependencies according to US practice. Support can be found in the original claims.

Claims 14, 15, and 33 are amended to rephrase the "use" claims as "method" claims according to US practice. Support can be found in the original claims.

Claim 2 is amended to include the word "isolated" with reference to the claimed nucleotide. Support can be found throughout the specification as filed, for example, at page 4, line 25 through page 5, line 6. Claim 2 is also amended to include language wherein SEQ ID NO:1 or the variants or portions thereof encode a polypeptide which retains the catalytic activity of the respective polypeptide encoded by the nucleic acid sequence of part a). Support can be found throughout the specification, for example at page 5, lines 8-17 and lines 27-29, and page 4, paragraph 2.

Claim 5 is amended to remove the word "contained" as suggested in the Office Action. Support can be found in the specification as filed, for example at page 5, line 21 through page 6, line 7 of the application as filed.

Claim 7 is amended to correct a typographical error. Support can be found for example at page 18, first full paragraph.

Claim 11 is amended to include the phrase "capable of hybridizing under stringent conditions with". Support for the phrase can be found at page 5, paragraph 3.

New claims 43-45 are added. Support can be found in the specification at page 13, last paragraph, and page 14, paragraphs 1 and 2, and for example in claims 4 and 5.

No new matter is entered.

Response to Restriction Requirement

In response to the new restriction requirement on page 3 of the Office Action, Applicants elect Group II (claims 2-15, 18-27, and 32) with traverse. Applicants further understand that the present election of Group II replaces the response filed by Applicants on October 16, 2006, and that the scope of examination is according to the restriction requirement on page 3 of the most recent Office Action, i.e. Group II (claims 2-15, 18-27, and 32).

The traversal is on the basis that the groups identified by the Office Action contain a special technical feature. For example, Groups II and III share the special technical feature of an isolated nucleic acid comprising a) a nucleic acid sequence encoding at least one non-ribosomal peptide synthetase which catalyse at least one step of the biosynthesis of safracins; b) a nucleic acid sequence which is complementary to the sequence in a); or c) variants or portions of the sequences of a) or b), where Group II is the isolated nucleic acid, and Group III

(claims 16 and 17) is the product encoded therein by the isolated nucleic acid. In addition, Group V (claim 33) is a method of use for the composition of claim 32 and therefore shares a special technical feature with claim 32, which is included in Group II. Finally, Applicants traverse the restriction requirement on the basis that it provides no basis for the withdrawal of claim 34.

Applicants traversed the restriction requirement of August 1, 2006 for failing to be based on the required lack of unity standard. In response, the Office Action of March 23, 2007 provides a new restriction requirement with a basis for restriction according to the lack of unity/special technical feature standard. Applicants were not provided an opportunity to make an election based on the new restriction requirement (either by telephone or by mailing of a restriction requirement). Rather, a first office action on the merits was included with the new restriction requirement. Applicants believe it would have been proper to withdraw the first restriction requirement, and request a response to the new restriction requirement (either by telephone or by mail) before proceeding with an examination on the merits. As Applicants were not permitted to respond to the restriction requirement prior to this paper, Applicants suggest that it would be improper, in the event of a subsequent rejection, for the next Office Action to be made "final". In addition, Applicants believe any subsequent rejection cannot be made final prior to an Office Action that clarifies the status of claim 34.

Objection to the Specification

The Office Action objects to the abstract of the specification due to an improper sentence structure, and suggests recitation of SEQ ID NO:1. In response, the abstract is amended to use the word "having" as suggested by the Office Action, and SEQ ID NO:1 is included in the abstract. Applicants respectfully request withdrawal of the objection.

Sequence Listing

The Office Action requires compliance with the sequence listing requirements. The Office Action refers to pages 49 and 24 of the specification.

With respect to page 49, an amendment to replace the paragraph on page 49 beginning "To overproduce P14..." with a duplicate paragraph including SEQ ID NOs was submitted at the time of entry of the national phase. Applicants believe the replacement paragraph meets the sequence listing requirements. In the event that the amendment to the paragraph on page 49 has not yet been entered, Applicants respectfully request the Examiner's assistance in entering the replacement paragraph submitted at the time of entry of the national phase.

With respect to page 24, Applicants request entry of the Sequence Listing submitted herewith. The content of the CRF and paper copies are the same. The Sequence Listing is amended to include SEQ ID NO:35. Support for SEQ ID NO:35 can be found on page 24, line 21, which discloses the sequence. In addition, the identifier "SEQ ID NO:19" is added to page 24 in order to comply with the sequence listing requirements. No new matter is entered. Applicants respectfully request withdrawal of the objection.

Drawings and July 19, 2006 IDS

Applicants thank the Examiner for the indication that the Drawings are accepted and the IDS of July 19, 2006 was considered.

Request for Corrected Filing Receipt / Priority Claim

Applicants request correction of the Filing Receipt to indicate the priority claim to GB 0229793.5, filed December 20, 2002. A marked up copy of the Filing Receipt is attached. The Inventor's Oath/Declaration filed on September 22, 2005 includes the priority claim. A certified copy of the foreign priority application is present in the image file wrapper (PAIR) for this application dated June 20, 2005. Applicants believe the requirements for claiming priority have been met and request the Examiner's assistance in updating the USPTO's records.

Claim Objections

Claims 11-15, 18-27, and 32 are objected to for improper multiple dependency. The claims are amended according to US practice. Applicants request withdrawal of the objection, and believe they are entitled to examination of claims 11-15, 18-27, and 32 on the merits.

Rejection Under 35 U.S.C. § 101

Claims 2-10 are rejected under 35 U.S.C. § 101 for failure to indicate the hand of the inventor. Claim 2 and, by dependency, all of the remaining examined claims, are amended to include the word "isolated" as suggested by the Examiner as being sufficient to overcome the rejection. Applicants request withdrawal of the rejection. With respect to the sentence in the rejection that claim 6 has improper dependency (Office Action, page 7, lines 15-16), Applicants request clarification of the statement.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 2-10 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement for the entire scope of the claims. The analysis includes a discussion of i) structure and function;

ii) conserved regions/domains, including predictability of the result of changes in structure; iii) state of the art; and iv) the unspecified amount of variants/derivatives of the protein, with the conclusion that the amount of guidance in each of the above categories is insufficient for purposes of enablement. Applicants respectfully traverse the analysis on the basis that for certain purposes where such guidance is necessary, the specification does provide sufficient guidance, and alternatively, on the basis that for certain other purposes, the guidance required by the Office Action is not necessary.

With respect to structure and function, the specification provides detailed information on the structure as claimed. For example, Claim 2 specifies SEQ ID NO:1, which is defined in the sequence listing. Sequence information is amenable to computer analysis with commercially-available software, such as DNA-Star, as discussed in the specification at page 24, lines 5-7. Therefore one of skill in the art, with SEQ ID NO:1 in hand, is provided detailed guidance with respect to the structures as claimed.

Regarding conserved regions/domains and predictability of the result of changes in structure, the Office Action indicates that

> predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to it function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification.

(Office Action, page 10, lines 1-10). However, the specification at page 12, lines 17-27 provides detailed information regarding highly conserved regions. Additional information regarding highly conserved regions is provided on page 14, line 8 through page 15, line 5. The detailed

information even identifies the activity of various active sites, such as the serine at the "site of thioester formation" at page 14, lines 19-22, and sites of ATP binding and hydrolysis. In addition, the specification provides information from knock-out mutants which provides additional information as to the types of changes that can be tolerated while maintaining activity (see specification, pages 19 and 20, and figures 5 and 6), i.e. due to the modular nature of the gene cluster, modular regions can be removed without affecting the activity of the remaining modular regions. Furthermore, with regard to the Office Action's requirement for maintaining the desired activity in the encoded protein, claim 2 and the claims which depend from claim 2 include the language wherein the variants or portions encode a polypeptide which retains the catalytic activity of the respective polypeptide encoded by the nucleic acid sequence of part a), and full complements thereof. With regard to the hybridization probes of claims 11-13, Applicants assert that such guidance is not necessarily required where the invention is a hybridization probe. Hybridization probes are known in the art, and described for example in the specification at page 5, lines 17-19, and page 6, lines 9-15. The use of hybrization probes can be seen in Example 2 and Table III in the specification. For hybridization probes, encoding a functional protein is not necessarily the desired use, and therefore, no such guidance is necessary. Therefore, one of skill in the art is provided with detailed information regarding conserved regions/domains, where such information is necessary.

With regard to the state of the art, Applicants bring to the Examiner's attention an example of engineered biosynthesis using a gene cluster (see attached IDS, which cites Tang et al., "Engineered Biosynthesis of Regioselectively Modified Aromatic Polyketides Using Bimodular Polyketide Synthases," PLOS Biology, Volume 2, Issue 2, pages 227-238, February 2004). As seen in the cited reference, examples of the modification of gene clusters for the

production of secondary metabolites are known. It is a well-accepted principle of patent law that those topics which are well-known in the art need not be repeated in the specification, and are preferably omitted. As a result of the high level of skill in the relevant field of engineered biosynthesis using gene clusters, the level of guidance required for enablement by the instant specification is correspondingly reduced.

Finally, with regard to the unspecified amount of variants/derivatives of the protein as discussed on pages 12-13 of the Office Action, Applicants assert that the scope of changes to, for example, SEQ ID NO:1 is not open-ended as suggested by the Office Action, and does not require "[m]aking and testing the infinite number of possible variants to find one that functions as described" (Office Action, page 13, lines 7-8). As noted above, Applicants provide detailed information on the structure of SEQ ID NO:1, on the conserved regions and active sites within SEQ ID NO:1, on the location, structure, and function of the modules contained within SEQ ID NO:1, and the nature of hybridization for probes to SEQ ID NO:1. All of this information, combined with the skill of the practitioner in the field of engineered biosynthesis using gene clusters, provides sufficient enablement.

Applicants respectfully request withdrawal of the rejection for lack of enablement.

Claims 2-10 are rejected under 35 U.S.C. § 112, first paragraph for lack of written description. The Office Action states that the claims "are directed to a genus of nucleic acids and proteins that are not adequately described as a skilled artisan cannot envision the detailed chemical structure of the derivatives encompassed in the claims," (Office Action, page 13, line 20 through page 14, line 1). Applicants respectfully traverse.

The specification fully describes SEQ ID NO:1 as a species within the genus as claimed. Furthermore, the common characteristics of additional species are identified in the claims, including such common characteristics as homology, hybridization, and biological activity of sequences within the genus (i.e. encoding proteins with homology to SEQ ID NOs 2-15). As noted above in the response to the enablement rejection, the specification provides detailed information on the conserved regions and active sites of the gene products.

The Office Action states

> The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*...The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred

(Office Action, page 15, lines 12-18, emphasis in original). Applicants note that "whatever is now claimed" in claims 2-10 is a genus of polynucleotides rather than polypeptides. Applicants have met the requirements of written description as provided in the Office Action, and respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 2-10 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Office Action suggests that amending claim 2 to include the term "full" will overcome the rejection of claim 2. Claim 2 is amended to include the phrase "fully complementary" in section b of the claim in accordance with the Examiner's suggestion.

Claim 5 is rejected based on the word "encoded" because "the gene encodes protein not other genes" (Office Action, page 16, paragraph 14). The word is amended to "contained" to show that the genes are contained in SEQ ID NO:1.

Claim 5 is rejected for the phrase "at least 30% identity" for not providing a reference sequence for the peptide. Applicants respectfully traverse, and note that the reference sequence for the peptide can be determined by the protein sequence that would be encoded by the nucleotides specified in the claim. Therefore, no separate listing is necessary.

Rejection Under 35 U.S.C. § 102(e)

Claims 2-6 and 8 are rejected under 35 U.S.C. § 102(e) as being anticipated by Rubenfield et al. (U.S. Patent 6,551,795, filed February 18, 1999). The rejection is "based on the broad recitation of variant or portion thereof," (Office Action, page 17, paragraph 15). The Office Action states that

> Rubenfield et al. teach a nucleic acid sequence derived from Pseudomonas and the encoding protein. Rubenfield et al. teach a sequence that is a portion or variant thereof for the claimed SEQ ID NO:1. Therefore, the limitations of the claims are met by the reference.

(Office Action, page 17, paragraph 15). Applicants respectfully traverse.

Applicants note that Rubenfield is 455 pages long. It is unclear which, if any, sequence from Rubenfield anticipates the instant claims. As such, Applicants are unable to determine where the anticipation in Rubenfield occurs. Because the Office Action does not specify which sequence in Rubenfield, if any, anticipates the instant claims, Applicants respectfully request withdrawal of the rejection. In addition, Applicants note that claim 2 is amended to include language wherein the variants or portions encode a polypeptide which retains the catalytic activity of the respective polypeptide encoded by the nucleic acid sequence of part a), and full complements thereof. Rubenfield fails to disclose variants or portions that retain the catalytic activity encoded by a nucleic acid sequence encoding at least one non-ribosomal peptide

synthetase which catalyse at least one step of the biosynthesis of safracins or the full complement thereof.

CONCLUSION

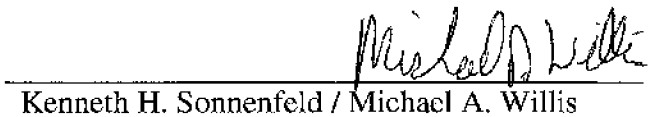
Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejections and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105008. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105008.

Respectfully submitted,
King & Spalding, LLP

Dated: September 13, 2007

By: 

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